APPENDIX C

TOXICITY CHARACTERISTICS OF GROUPS OF ANALYTES

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Many chemicals on the list of target analytes (see Table 1-1 in Section 1) fall into two groups: organochlorine pesticides and organophosphate pesticides. Chemicals in these groups, while having many individual characteristics, have multiple toxicity attributes in common with other members of the same group due to their structural similarity. Rather than listing all aspects of the toxicity of each member under the individual chemical discussions, those characteristics shared by members of the group are listed in this appendix.

The following information is of a qualitative nature and includes the spectrum from acute high-dose responses to chronic exposure low-dose responses. This range was included for a number of reasons. Individual responses to chemical exposures will vary considerably. It is not anticipated that all people exposed at the same dose will respond in the same manner. Those individuals who are chemically sensitive may respond to chronic low doses as severely as less sensitive individuals who are exposed to high doses. Second, the effects elicited by organophosphate and organochlorine pesticides can be characterized on a continuum for many organ systems (e.g., nervous system effects, liver damage). Therefore, many effects are associated with both acute and chronic exposure. Finally, there are very limited dose-response data establishing specific human thresholds for effects to occur. The risk values (reference doses), derived primarily from animal studies, do not predict the exposure level at which response will occur, but rather incorporate uncertainty factors with the study data to determine a level at which no one is anticipated to experience adverse effects. Consequently, it is not possible, in most cases, to provide quantitative data regarding the dose associated with a specific level of effect in a specific organ system. Under most circumstances it is assumed that the very severe effects such as convulsions, coma, and death are associated with acute high-level exposures to chemicals. The information provided below was obtained from the following sources (full citations are provided at the end of this appendix):

- *Recognition and Management of Pesticide Poisonings* (U.S. EPA, 1982)
- *Casarett and Doull's Toxicology* (Klaassen et al., 1986)
- *Pesticides and Human Health* (Cunningham-Burns and Hallenbeck, 1984)
- *Pesticides Studied in Man* (Hayes, 1982)
- *Handbook of Pesticide Toxicology* (Hayes and Laws, 1991).

In addition, the Hazardous Substances Data Bank (HSDB, 1993), which was consulted for specific information on target analytes, contains general clinical

effects information for organophosphate exposures and organochlorine exposures that was used in the development of this appendix.

C.1 Organochlorine Pesticides

Organochlorine pesticides are readily absorbed via the digestive system. They often accumulate in fatty tissue, including brain and adipose tissue, and may also be found in human milk due to its high lipid content. The neurological effects of organochlorine exposure are based upon interference with axonic transmission of nerve impulses. This causes altered functioning of the nervous system, primarily the brain.

The following symptoms are commonly associated with exposure to organochlorines: behavioral changes, sensory and equilibrium disturbances, involuntary muscle activity, depression of vital centers (particularly those controlling respiration), myocardial irritability, tremor, twitching, nausea, confusion, apprehension, excitability, dizziness, headache, disorientation, weakness, paresthesias, convulsions, and unconsciousness (HSDB, 1993; U.S. EPA, 1982).

Organochlorines stimulate synthesis of hepatic drug-metabolizing microsomal enzymes, primarily in the liver; however, they do so in different ways (Hayes and Laws, 1991, p. 739). Many organochlorines are associated with liver and kidney toxicity. Organochlorine pesticides' induction of the hepatic microsomal enzyme system causes alterations in the rate of metabolism of all other endogenous or exogenous chemicals metabolized by this system. Metabolism may detoxify or increase the toxicity of chemicals, depending on whether the parent or metabolite is more toxic. For example, DDT is reported to promote some tumorigenic agents and antagonize others as a result of the induction of microsomal enzymes (ATSDR, 1992). In addition, exposure to other chemicals that induce the same enzymes may increase the toxicity of the chemical under evaluation by enhancing its metabolism to its toxic intermediate.

The induction of microsomal enzymes by organochlorines has serious implications for the metabolism of some pharmaceutical drugs. Alterations in response to drugs have been observed both in humans and experimental animals. For example, increased phenobarbital metabolism resulting from an increased body burden of DDT (10 µg) led to a 25 percent decrease in effectiveness of the drug in experimental animals (HSDB, 1993). Concern regarding interaction with drugs is indicated in discussions of especially susceptible populations in the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles. For example, due to the interactive effects of chlordane with other chemicals via microsomal enzymes, ATSDR has cautioned that: "doses of therapeutic drugs and hormones may require adjustment in patients exposed to chlordane" (ATSDR, 1992a). A similar caution is provided for DDT and its analogs: individuals who use medications that involve the mixed function oxidase system (MFO inhibitors) directly or for metabolic processes may be at risk for alteration of the drugs' efficacy and/or timing if they are exposed to DDT (ATSDR, 1992b).

For most chemicals, information was not available on the quantitative relationships between various pharmaceuticals and organochlorine body burdens or intakes. When information was located on these types of interactions, it was included in the chemical discussions. For more information on this, the reader is referred to the ATSDR Toxicological Profiles and to the open literature.

C.2 Organophosphate Pesticides

Organophosphates are efficiently absorbed via ingestion. Their toxicity depends in part on the rate at which the chemicals are metabolized in the body. This occurs principally by hydrolysis to nontoxic or minimally toxic byproducts. The most studied and obvious effect of organophosphate poisoning is cholinesterase inhibition. This results from phosphorylation of the acetylcholinesterase enzyme at nerve endings. Loss of enzyme function allows accumulation of acetylcholine (the neurotransmitter) at cholinergic neuroeffector junctions, causing muscarinic effects, and at skeletal myoneural junctions, and in autonomic ganglia (nicotinic effects). Organophosphates cause central nervous system (CNS) disturbances through impairments of nerve impulse transmission in the brain (U.S. EPA, 1982).

It is not clear what, if any, adverse effects are associated with exposure at levels that produce only cholinesterase inhibition in the absence of any other effects. This is currently under evaluation at EPA. In 1993, EPA's Scientific Advisory Board (SAB) issued a report on cholinesterase inhibition and risk assessment (U.S. EPA, 1993). A key finding was:

> To date, analyses of studies of cholinesterase inhibition in plasma and in red blood cells do not provide information useful for evaluating potential hazards and risks in the nervous system. This finding justifies a new science policy against the use of blood cholinesterase inhibition data for risk assessment purposes. (U.S. EPA, 1993)

Multiple adverse effects resulting from cholinesterase inhibition and other toxic mechanisms have been associated with organophosphate exposure. The SAB report states that:

> Clinical effects associated with exposure to cholinesterase inhibitors can be used in risk assessment to define hazard and to calculate benchmark doses and RfDs. (U.S. EPA, 1993)

Although the issue may be clearer for clinical effects, there has not, as yet, been resolution of the question as to whether cholinesterase inhibition alone should be used as a critical endpoint. The 1993 report "does not provide a simple yes or no answer to the issue of using RBC cholinesterase inhibition data by itself (i.e., in the absence of clinical symptoms) for risk assessment." Concern arises, in part, from the fact that blood enzyme inhibition may precede and predict brain enzyme inhibition, which is of significant concern (U.S. EPA, 1993). Additional information is required to clarify this issue.

The SAB report suggests that EPA continue research designed to evaluate the correlation of clinical signs with blood cholinesterase inhibition, especially correlations with respect to dose, time, and linearity (U.S. EPA, 1993). Cholinesterase inhibition has been used as the critical endpoint, on which RfD calculations are based, for many organophosphates included in the IRIS database. Because of the uncertainty surrounding the use of cholinesterase inhibition as an effect, readers may wish to calculate their own exposure limits. When the RfD for the target analytes is based on cholinesterase inhibition, other chronic toxicity data are provided for analytes having sufficient data. This enables the reader to calculate estimated exposure limits (using Equations 3-1 and 3-3 in Section 3 of this report) and derive fish consumption limits (using Equation 3-2 in Section 3) based on other health endpoints if appropriate.

Effects commonly associated with organophosphate exposure include the following: headache, dizziness, weakness, incoordination, muscle twitching, tremor, nausea, abdominal cramps, diarrhea, sweating, blurred or dark vision, confusion, tightness in the chest, wheezing, productive cough, pulmonary edema, slow heartbeat, salivation, tearing, toxic psychosis with manic or bizarre behavior, influenza-like illness with weakness, anorexia, malaise, incontinence, unconsciousness, and convulsions (HSDB, 1993; U.S. EPA, 1982). In addition, some, but not all, organophosphates cause peripheral neuropathy resulting from demyelination of the nerves. Specific effects include numbness, tingling, pain, weakness, and paralysis in the arms and legs. These effects may be delayed and may be reversible or irreversible (U.S. EPA, 1982).

Muscarinic effects in children exposed to organophosphates may differ from those in adults. Those most commonly encountered with acute exposure include: CNS depression, stupor, flaccidity, dyspnea, and coma. Seizures may be more common in children than in adults (HSDB, 1993).

Psychiatric symptoms that have been reported include defects in expressive language and cognitive function, impaired memory, depression, anxiety or irritability, and psychosis. These are more common in individuals with other clinical signs of organophosphate poisoning or with preexisting psychological conditions (HSDB, 1993). Behavioral effects are a prominent concern based on the results of toxicity data reviewed for the target analytes. It appears to be one of the most sensitive indicators of toxicity related to chronic exposure. Behavioral effects, such as aggressiveness, irritability, and hyperactivity, occurred at low levels of exposure in animal studies. These effects are particularly problematic because they are difficult to specifically associate with organophosphate exposure in the human population but could have serious consequences.

There is a recognized high-risk human population with respect to organophosphate exposure. Approximately 3 percent of the human population has an abnormally low plasma cholinesterase level resulting from genetic causes. These people are particularly vulnerable to cholinesterase-inhibiting pesticides. Others at greater risk include: persons with advanced liver disease, malnutrition, chronic alcoholism, and dermatomyositis, because they exhibit chronically low plasma

cholinesterase activities. Red blood cell (RBC) acetylcholinesterase is reduced in certain conditions such as hemolytic anemias; people with these conditions are at greater risk than the general population from exposure to organophosphates (U.S. EPA, 1982).

Compounds known to reduce plasma pseudocholinesterase activity and thereby aggravate the effects of cholinesterase inhibitors are carbon disulfide, benzalkonium salts, organic mercury compounds, ciguatoxins, and solanines (U.S. EPA, 1982).

The Hazardous Substances Data Bank (HSDB, 1993) contains a summary of diseases and disorders that are of special concern for individuals exposed to organophosphates. The following are listed as contraindications for work with (and exposure to) these chemicals: “organic diseases of the CNS, mental disorders and epilepsy, pronounced endocrine and vegetative disorders, pulmonary tuberculosis, bronchial asthma, chronic respiratory diseases, cardiovascular diseases and circulatory disorders, gastrointestinal diseases (peptic ulcer), gastroenterocolitis, diseases of the liver and kidneys, and eye diseases (chronic conjunctivitis and keratitis)” (HSDB, 1993).

C.3 REFERENCES

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